mailed May 7, 2003 (Paper No. 23). This rejection is respectfully traversed. As an initial matter, claims 5-8 have been cancelled, thus obviating the rejection of that claim.

The examiner states that "[c]laim 5 recites the term 'cancer cell specific identifying agent'; however, there does not appear to be proper and sufficient antecedent basis in the specification to support the recitation of this term in the claims". The examiner also further states, "...the examples of identifying agents set forth in the disclosures on pages 14 and 15 do not provide adequate support for the breath of the claim language. In particular, the disclosed examples of identifying agents fail to provide the necessary express, implicit, or inherent support because, for example, the identifying agents that are antibodies bind antigens, such as ErbB-2, which are not cancer specific." The Applicants respectfully disagree.

The term "cancer cell specific identifying agent" is fully supported by the specification. In particular, the specification describes potential identifying agents as, among others, "...monoclonal antibodies or other molecules directed against over expressed or stage-specific cellular epitopes..." (see page 10, lines 25-26). The specification also provides a list of publications which describe specific examples of such molecules and their use such as antibodies for 44-3A6, A-80, DF3, H23, and CEA antigens as well as numerous others agents (see page 15, lines 5-23). In response, the examiner states that "...the examples set forth in the disclosures on page 14 and 15 do not provide adequate support for the breath of the claim language. In particular, the disclosed examples of identifying agents fail to provide the necessary express, implicit, or inherent support because, for example, the identifying agents are antibodies bind antigens, such as ErbB-2, which are not cancer specific". The Applicants respectfully disagree.

Using the examiner's own definition of "specific" (see Paper No. 28, page 10), a "cancer cell specific identifying agent" is one that would be reasonably defined as an identifying agent that distinguishes a breast cancer cell from normal breast cell. Clearly, the examples of identifying agents set out in the specification, such as ErbB-2, can differentiate between normal and cancerous breast cells.

Although Applicants submit that the term "cancer cell specific identifying agent" has proper and sufficient antecedent basis in the specification to support the recitation of this term in the claims and would be clearly recognized by one of skill in the art, in order to expedite prosecution, claims 5-8 have been cancelled thereby obviating the rejection. Accordingly, for the

reasons stated above, the rejection under 35 U.S.C. § 112, first paragraph, for lack of written description should not be applied to the newly submitted claims 33-48.

The Rejections of Claims 1-16 Under 35 U.S.C. §112, First Paragraph Should be Withdrawn:

Claims 1-16 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The examiner states that "[c]laims 1, 5, 9, and 13 recite, 'allowing [...] unbound portions of the delivered [compound or identifying agent] to be eliminated from said at least one duct'. Additionally, claims 9 and 13 recite, 'determining the lymph node involvement after said unbound portion of the delivered [compound or identifying agent] are no longer present within said at least one breast duct'. However, there does not appear to be proper and sufficient antecedent basis in the specification to support the recitation of this term in the claims." Although the Applicants disagree that the removal of non-specifically bound compound is limited by the specification to an active versus a passive process, in order to expedite prosecution claims 9-16 have been cancelled thereby obviating the rejection. Accordingly, for the reasons stated above, the rejection under 35 U.S.C. § 112, first paragraph, for lack of written description should not be applied to the newly submitted claims 33-48.

The Rejections of Claims 9-16 Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn:

Claims 9-16 were rejected under 35 U.S.C. §112, second paragraph, as being incomplete. The examiner states "...claims 9 and 13 omit one or more essential steps, such omission amounting to a gap between the steps for the reason stated in section 12 of the previous Office Action mailed May 7, 2003 (Paper No. 26)." Claims 9-16 have been cancelled to expedite prosecution, thereby obviating the rejection. Accordingly, for the reasons stated above, the rejection under 35 U.S.C. § 112, second paragraph should not be applied to the newly submitted claims 33-48.

The Rejection of Claims 5-8 Under 35 U.S.C. §103(a) Should be Withdrawn:

Claims 5-8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Hou *et*

al. in view of Canto *et al.* The examiner states "In view of the prior art, as a whole, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Hou *et al.* to detect in a breast duct or breast ductal network, the presence of premalignant or malignant breast cancer cells, which are bound by an identifying agent, after washing the breast tissue to remove an unbound, or non-specifically bound identifying agent and/or after allowing any unbound bound [sic] identifying agent to passively diffuse out of the tissue, because Canto *et al.*, for example, teaches that before detecting premalignant or malignant cells bound to the identifying agent, the excess, unbound identifying agent should be washed away from the anatomical site of the suspected lesion and it would have been understood by the artisan of ordinary skill at the time of invention that the presence of unbound or non-specifically bound identifying agent in the tissue might produce undesirable levels of background, obscure detection of the premalignant or malignant cells within the tissue, and lead to false negative and/or false positive results." The Applicants respectfully disagree.

Hou *et al.* discloses a method of preparing a breast duct for galactography. Hou *et al.* does not teach the use of a compound comprising a targeting agent coupled to an identifying agent for identifying the location of either premalignant or malignant breast duct cells. The examiner states "Hou *et al.* teaches a method comprising providing a pre-malignant or malignant cancer cell specific identifying agent, namely methylene blue. Hou *et al.* teaches delivering the identifying agent through at least one breast duct by cannulation or catheterization of the [sic] one or more breast ducts." The Applicants strongly disagree. Hou *et al.* teaches the use of methylene blue to identify only the location a breast duct. Nowhere in the article is it disclosed or suggested that methylene blue may be used to identify premalignant or malignant cells. Thus Hou *et al.* cannot anticipate any of the pending claims because it does not disclose all of the limitations of the pending claims.

Canto *et al.* discloses a method of selectively staining intestinal metaplasia in Barrett's esophagus with methylene blue. The examiner states "Canto *et al.* teaches methylene blue is capable of binding selectively to pre-malignant, or dysplastic cells, and to malignant cells. Therefore, because methylene blue selectively stains pre-malignant or malignant tissue differentially relative to normal tissue within the breast duct or breast ductal network and enables clinician [sic] to distinguish pre-cancerous and cancerous tissue from normal tissue within the

breast duct or breast ductal network, it would appear that methylene blue is a 'cancer cell specific identifying agent that is cancer cell specific within the breast duct or breast ductal network', as recited in claim 5." The Applicants respectfully disagree.

Canto *et al.* teaches the use of methylene blue to stain specialized columnar epithelium in the esophagus of patients to identify adenocarcinomas. Canto *et al.* does not teach the use of methylene blue to stain premalignant or malignant cells. In fact, Canto *et al.* states "[p]ositive staining was defined as blue-stained endoscopically normal esophageal mucosa that persisted despite vigorous water irrigation." (see page 2, column 2). The examiner then goes on to state, "Canto *et al.* demonstrates that methylene blue can be used to distinguish and localize premalignant or malignant epithelial cancer cells." This is incorrect. Canto *et al.* teaches that methylene blue can be used to stain normal columnar epithelial which is located in the esophageal mucosa. Canto *et al.* does not teach that methylene blue can be used as a stain to distinguish between premalignant or malignant cancer cells in breast ducts. Even assuming *arguendo* that methylene blue can be used to distinguish premalignant or malignant cancerous tissue from normal tissue, claim 5 includes the step of "allowing the delivered identifying agent to bind to premalignant or malignant cells within said at least one duct or ductal network...". Methylene blue does not specifically bind to premalignant or malignant cancerous cells. Thus Canto *et al.* cannot anticipate any of the pending claims because it does not disclose all of the limitations of the pending claims.

In order to establish *prima facie* obviousness of a claim, all of the limitations of the claims must be taught or suggested by the prior art. *In re Royka* 490 F.2d 981 (CCPA 1974). For all the reasons stated above, the combination of Hou *et al.* and Canto *et al.* does not meet this standard is not sufficient to establish *prima facie* obviousness.

Although the Applicants believe that the rejections of claims 5-8 under 35 U.S.C. §103(a) are improper, in order to expedite prosecution, claims 5-8 have been cancelled thereby obviating the rejection. Accordingly, for the reasons stated above, the rejection of claims under 35 U.S.C. §103(a) as being unpatentable over Hou *et al.* in view of Canto *et al.* should not be applied to the newly submitted claims 33-48.

The Rejection of Claims 1-4, and 9-16 Under 35 U.S.C. §103(a) Should be Withdrawn:

Claims 1-4, and 9-16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Allan *et al.* in view of Krag *et al.*, Hou *et al.*, Canto *et al.*, and Vitetta *et al.* The Examiner is of the opinion that "...it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Allan *et al.*, by delivering the identifying agent through at least one breast duct according to the method of Hou *et al.*, because Vitetta *et al.*, teaches monoclonal antibodies, which are administered to a patient intravenously, may not be able to gain access to a tumor because, for example, the tumor may be poorly vascularized, whereas monoclonal antibodies comprising an identifying agent, which are administered through one or more breast ducts, are delivered to the precise location of the suspected cancerous lesions in the breast duct and breast ductal network, such that the monoclonal antibody can make contact [sic] the cancerous lesion without need of passing through the blood." Applicants respectfully disagree.

The examiner has failed to establish a *prima facie* case of obviousness, since Allan *et al.* Krag *et al.*, Hou *et al.*, Canto *et al.*, and Vitetta *et al.*, alone or in combination, fail to teach or suggest the claimed invention and further fail to provide the necessary motivation or expectation of success for the ordinarily skilled artisan to arrive at the claimed invention.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g.*, *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and*

Refractories, Inc., 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

A new combination of elements can be patented "whether it be composed of elements all new, partly new or all old." *Rosmount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546, 221 USPQ 1, 7 (CAFC 1984). The Court of Appeals for the Federal Circuit has forcefully stated that a claim rejection must provide a specific motivation in the art for combining elements from cited art in order to establish obviousness of a new combination.

> "[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. ... [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular. ... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.' ... [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination ... to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed. Cir. 1999), emphasis added.

Dembiczak involved patent claims to "a large trash bag made of orange plastic and decorated with lines and facial features, allowing the bag, when filled with trash or leaves, to resemble a Halloween-style pumpkin, or jack-o'-lantern." *Dembiczak*, 996, 1616. The prior art cited by the Board included: a book describing how to teach children to make a "Crepe Paper Jack-O-Lantern;" a book describing a method of making a "paper bag pumpkin" by stuffing a bag with newspapers, painting it orange, and then painting on facial features with black paint; a U.S. Patent describing a bag apparatus wherein the bag closure is accomplished by the use of folds or gussets in the bag material; design patents issued to Dembiczak; and prior art "conventional" plastic lawn or trash bags. The Federal Circuit held that the claimed pumpkin-style trash bag was not obvious because there was no clear, particular motivation to combine the cited references.

This holding of *Dembiczak* that evidence of motivation to combine must be clear and particular to establish obviousness has been emphasized over and over again by the Federal

Circuit since *Dembiczak* was decided. It was strongly reemphasized in *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161 (Fed. Cir. 2000):

> In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. See, e.g., In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("[T]he Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617 ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). "Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness." Sibia Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000); Tec Air, Inc. v. Denso Mfg., Inc., 192 F.3d 1353, 1359, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with those of another reference).
>
> ... there is "a general rule that combination claims can consist of combinations of old elements as well as new elements," Clearstream Wastewater Sys. v. Hydro-Action, Inc., 206 F.3d 1440, 1446, 54 USPQ2d 1185, 1189-90 (Fed. Cir. 2000), "[t]he notion . . . that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1575, 1 USPQ2d 1593, 1603 (Fed. Cir. 1987); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) ("It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements."). *Ruiz* at 1167

The motivation cited in the Office Action for the proposed combination is as follows:

> One would have been motivated to modify the method of Allan *et al.*, by delivering the identifying agent using the method of Hou *et al.*, because the modification would provide an advantage to the clinician because delivering the identifying agent according to the method of Hou *et al.*, enables one to deliver the identifying agent directly to the target site at which the cells are expected to occur in a patient without undue risk of retention of the identifying agent in tissues where the cells are not expected to be found and without undue risk that at least a portion of the identifying agent will naturally clear the patient's body before it reaches the breast ductal network via the blood stream, as might occur if the identifying agent were administered intravenously. Furthermore, one would have been motivated to modify

> the method of Allan *et al.*, by delivering the identifying agent using the method of Hou *et al.*, because the modification would provide an additional advantage to the clinician, because the clinician could image the tumor without risking harm to the patient by having to deliver unnecessary large quantities of antibodies and radioisotopes that may have adverse effects." (Office Action at pages 20-21)

This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required under *In re Dembiczak*. The claims here are no more obvious than those at issue in *Dembiczak*. No clear, particular suggestion or motivation in the prior art to anticipate the specific methods recited in claims 1, 9, and 13, much less for the claims dependent thereon with their additional limitations.

Allan *et al.*, discloses a radiolabelled monoclonal antibody to localize tumor deposits displaying the target antigen, c-erbB2. Allan *et al.* does not teach a method of delivering an agent through at least one breast duct. Furthermore, Allan *et al.* and Hou *et al.* cannot properly be combined. Allan *et al.* explicitly teaches away from the administration of the c-erbB2 antibody via any other (such as ductal) route. In fact, the last paragraph of the summary in Allan *et al.* states that "[t]he good performance of this radiolabelled antibody with patients that strongly stain for the antigen encourages the development of this system as both a method of staging breast cancer and a potential means of immunotherapy in this subgroup of patients" (emphasis added). There is simply no suggestion to modify the method described in Allan *et al.* such that the c-erbB2 antibody is administered through a breast duct. As mentioned previously, Applicants disagree with the examiner's assessment of Hou *et al.* Hou *et al.* discloses a method of preparing a breast duct for galactography, not a method for imaging or staging breast cancer. Hou *et al.* also does not disclose the use of a compound specifically bound to premalignant or malignant cells for the purpose of identifying the location of either premalignant or malignant breast duct cells in a breast duct or breast ductal network.

The obviousness rejection is clearly based on hindsight from these disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention. As for motivation to combine, the examiner states "...one would

have been motivated to modify the method of Allan *et al.*, by delivering the identifying agent using the method of Hou *et al.*, because the modification would provide an additional advantage to the clinician, because the clinician could image the tumor without risking harm to the patient by having to deliver unnecessary large quantities of antibodies and radioisotopes that may have adverse effects." The examiner provides no support for such a statement. As stated in *Dembiczak*, "...[b]road conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" Absent some teaching or suggestion in the prior art to combine the elements, there is no clear, particular motivation to reach the claimed invention.

Applicants respectfully submit that the Examiner has, at most, set forth an "obvious to try" rationale in support of this obviousness rejection. However, an "obvious to try" rationale is not the appropriate standard for obviousness under 35 U.S.C. §103 (M.P.E.P. §2145).

Applicants submit that combination of Allan *et al.* Krag *et al.*, Hou *et al.*, Canto *et al.*, and Vitetta *et al.*, do not together teach or suggest all of the limitations of the claims nor do the publications cited in the previous and present Office Actions, singly or in combination, suggest developing the methods of the present invention.

Finally, Applicants respectfully submit that the Examiner's combination of rejections appears inconsistent in asserting that the claimed methods are both obvious under 35 U.S.C. § 103 in view of a number of cancer cell specific identifying agents, such as ErbB-2, and at the same time non-enabled under 35 U.S.C. § 112, first paragraph because "the disclosed examples of identifying agents fail to provide the necessary express, implicit, or inherent support because, for example, the identifying agents that are antibodies bind antigens, such as ErbB-2, which are not cancer specific." Applicants, therefore, respectfully request reconsideration and withdrawal of the rejections as inconsistent.

Although the Applicants believe that the rejections of claims 1-4, and 9-16 under 35 U.S.C. §103(a) are improper, in order to expedite prosecution, claims 1-4, and 9-16 have been

cancelled thereby obviating the rejection. Accordingly, for the reasons stated above, the rejection of claims under 35 U.S.C. §103(a) as being unpatentable over Allan *et al.* in view of Krag *et al.*, Hou *et al.*, Canto *et al.*, and Vitetta *et al.* should not be applied to the newly submitted claims 33-48.

The Rejection of Claims 1-16 Under 35 U.S.C. §103(a) Should be Withdrawn:

Claims 1-16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over USP 6,168,779 (hereinafter referred to as '779) in view of Canto *et al.*, Allan *et al.*, as evidenced by Krag *et al.* and Lasfargues *et al.* The Examiner is of the opinion that "...it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that an anti-Erb2 antibody coupled to an identifying agent that specifically targets cancerous epithelial cells that over-express ErbB-2 within the breast duct can be used in the method of '779 to identify the location of malignant breast cancer within a breast duct or breast ductal network." The Applicants respectfully disagree.

As mentioned previously, Allan *et al.*, discloses a radiolabelled monoclonal antibody to localize tumor deposits displaying the target antigen, c-erbB2. Allan *et al.* does not teach a method of delivering an agent through at least one breast duct. Furthermore, Allan *et al.* and USP 6,168,779 cannot properly be combined. As mentioned above, Allan *et al.* explicitly teaches away from the administration of the c-erbB2 antibody via any other (such as ductal) route. There is simply no suggestion to modify the method described in Allan *et al.* such that the c-erbB2 antibody is administered through a breast duct. Similarly, the teaching of Lasfargues *et al.* does not describe a method of administering a compound through a breast duct. In fact, Lasfargues *et al.* does not even describe an *in vivo* methodology, but instead describes a protocol for culturing solid breast carcinomas *in vitro*.

The obviousness rejection is clearly based on hindsight from these disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention. As for motivation to combine, the examiner states "...one would have been motivated to use the identifying agent of Allan *et al.* in the method of '779 to identify of [sic] the location of malignant breast cancer cells expressing ErbB2 within the duct of a

patient's breast and to determine whether or not there is lymph node involvement in the patient". The examiner provides no support for such a statement. As stated in *Dembiczak*, "...[b]road conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" There is no mention in either Allan *et al.* nor '779 of the advantages of administering a compound through a breast duct to locate premalignant or malignant cells in a breast duct or in its associated lymph node. Absent some teaching or suggestion in the prior art to combine the elements, there is no clear, particular motivation to reach the claimed invention.

Applicants respectfully submit that the Examiner has, at most, set forth an "obvious to try" rationale in support of this obviousness rejection. However, an "obvious to try" rationale is not the appropriate standard for obviousness under 35 U.S.C. §103 (M.P.E.P. §2145).

Applicants submit that combination of Allan *et al.* Krag *et al.*, Lasfargues *et al.*, and Canto *et al.*, do not singly or in combination, suggest developing the methods of the present invention.

Finally, Applicants respectfully submit that the Examiner's combination of rejections appears inconsistent in asserting that the claimed methods are both obvious under 35 U.S.C. § 103 in view of a number of cancer cell specific identifying agents, such as ErbB-2, and at the same time non-enabled under 35 U.S.C. § 112, first paragraph because "the disclosed examples of identifying agents fail to provide the necessary express, implicit, or inherent support because, for example, the identifying agents that are antibodies bind antigens, such as ErbB-2, which are not cancer specific." Applicants, therefore, respectfully request reconsideration and withdrawal of the rejections as inconsistent.

Although the Applicants believe that the rejections of claims 1-16 under 35 U.S.C. §103(a) are improper, in order to expedite prosecution, claims 1-16 have been cancelled thereby obviating the rejection. Accordingly, for the reasons stated above, the rejection of claims under 35 U.S.C. §103(a) as being unpatentable over USP 6,168,779 in view of Canto *et al.*, Allan *et al.*, as evidenced by Krag *et al.* and Lasfargues *et al.* should not be applied to the newly submitted claims 33-48.

The Rejection of Claims 1-4 and 9-16 Under 35 U.S.C. §103(a) Should be Withdrawn:

Claims 1-4 and 9-16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Hou *et al.* in view of Canto *et al.*, McQuarrie *et al.*, and Krag *et al.* The examiner states "Given the teachings of the prior art, as a whole, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the radiolabelled antibody of McQuarrie *et al.*, for the contrast agent of Hou *et al.*, in the method of Hou *et al.* in order to identify the location of malignant breast cancer in the body of a patient, because Hou et al. teaches a method of delivering the antibody directly to the anatomical site where the clinician expects to find cancerous cells and thus, requires less antibody be administered to the patient since not a much of the antibody will be absorbed by non-targeted tissues (e.g., the kidneys) and because McQuarrie *et al.* teaches that the antibody can be used successfully to localize malignant breast cancer in a patient since unbound antibody is absorbed and cleared in the body of the patient." The Applicants respectfully disagree.

As mentioned above, Hou *et al.* discloses a method of preparing a breast duct for galactography. Hou *et al.* does not teach the use of a compound comprising a targeting agent coupled to an identifying agent for identifying the location of either premalignant or malignant breast duct cells. McQuarrie *et al.* teaches the injection of a monoclonal antibody 170H.82 labeled with technetium-99m for radioimmunoscintigraphy in patients with breast adenocarcinoma. McQuarrie *et al.*, like Allan *et al. above,* does not teach a method of delivering an agent through at least one breast duct. Furthermore, McQuarrie *et al.* and Hou *et al.* cannot properly be combined. McQuarrie *et al.* explicitly teaches away from the administration of an antibody via any other (such as ductal) route. As stated in McQuarrie *et al.*, "[o]verall, RIS with 99mTc-Mab-170H.82 shows promise, and confirms the results of our initial pilot study." There is no mention in McQuarrie *et al.* of a concern of accumulation of the radiolabelled antibody in non-targeted tissues. The examiner is of the opinion that such motivation exists by stating "[o]ne would have been motivated to substitute the radiolabelled antibody of McQuarrie *et al.* for the contrast agent of Hou *et al.* in the method of Hou *et al.* because the specificity of the antibody will enable superior accuracy in localizing the malignancy for the purpose of excising the diseased tissue and because the antibody does not have to be removed by the practitioner form the body of the patient, thus simplifying the procedure." The examiner provides no support for

such a statement.

As mentioned previously, Hou *et al.* teaches the use of methylene blue to identify only the location a breast duct. Nowhere in the article is it disclosed or suggested that methylene blue may be used to identify premalignant or malignant cells. Thus Hou *et al.* cannot anticipate any of the pending claims because it does not disclose all of the limitations of the pending claims. Likewise, McQuarrie *et al.* does not describe a method administering a compound through a breast duct for locating the presence of premalignant or malignant cells in a breast duct or associated lymph nodes. There is no mention in either Hou *et al.* nor McQuarrie *et al.* of the advantages of administering a compound through a breast duct to locate premalignant or malignant cells in a breast duct or in its associated lymph node. Absent some teaching or suggestion in the prior art to combine the elements, there is no clear, particular motivation to reach the claimed invention.

Applicants respectfully submit that the Examiner has, at most, set forth an "obvious to try" rationale in support of this obviousness rejection. However, an "obvious to try" rationale is not the appropriate standard for obviousness under 35 U.S.C. §103 (M.P.E.P. §2145).

Applicants submit that combination of Hou *et al.*, Canto *et al.*, McQuarrie *et al.*, and Krag *et al.*, do not singly or in combination, suggest developing the methods of the present invention.

Although the Applicants believe that the rejections of claims 1-4 and 9-16 under 35 U.S.C. §103(a) are improper, in order to expedite prosecution, claims 1-4 and 9-16 have been cancelled thereby obviating the rejection. Accordingly, for the reasons stated above, the rejection of claims under 35 U.S.C. §103(a) as being unpatentable over Hou *et al.* in view of Canto *et al.*, McQuarrie *et al.*, and Krag *et al.* should not be applied to the newly submitted claims 33-48.

Provisional Rejection of Claims 1-16 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting:

Applicants reiterate that a terminal disclaimer may be filed at the time the claims are indicated to be allowable. Applicants appreciate the examiner holding this issue in abeyance until such a time that there is allowable subject matter.

CONCLUSION

In light of the amendments and arguments presented above, Applicants respectfully submit that the claims are in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 502855 referencing attorney docket number 12.006011.

Respectfully submitted,

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